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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,840	KIKUCHI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *10,11,14,15 and 17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12,13,16,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *attachment/West English Equivalent*.

DETAILED ACTION

1. Claims 1-22 are pending.

2. Applicant's election with traverse of Group I, claims 1-16 and 21-22 directed to a humanized antibody binding to CD47 and a therapeutic agent thereof and the humanized MABL-2 antibody HL5, SEQ ID NOs: 73, 37 and 7 as the species, filed on 12/08/08, is acknowledged.

Applicant's traversal is on the grounds that as all species sequences in the specification referring to CDRs have a common basis in binding CD47. This is not found persuasive because theses sequences are distinct species because their structures and modes of action are different which, in turn, address different therapeutic endpoints. It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. See MPEP 803.04. Further, searches of all the sequences would place an undue burden upon the examiner due to the distinct and divergent subject matter of each species. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 10-11, 14-15 (non-elected species), 17-20 (non-elected Group) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-9, 12-13, 16 and 21-22 are under examination as they read on a humanized antibody binding to CD47 and a therapeutic agent thereof and the humanized MABL-2 antibody HL5, SEQ ID NOs: 73, 37 and 7 as the species.

5. Applicant's IDS, filed 5/10/2006, is acknowledged, however, references A10-A14 were crossed out as English translation of the references were not found. Applicant is invited to produce such documents.

6. The specification is objected to because it refers to multiple amino acid residues positions that represented by a nucleic acid sequences to identify the amino acid residues. For example, page 3, lines 27-28 to page 4, line 1 discloses the sequence of aa 31-35 (CDR1), the sequence of aa 50-66 (CDR2), and the sequence of aa 99-106 (CDR3) of SEQ ID NO: 7. However, SEQ ID NO: 7 is a nucleic acid sequence and is limited to its nucleic acid component. This issue is true for all through the specification. Applicant's cooperation is requested in correcting all the sequence misrepresentation in the specification.

7. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 51, line 16-17 has described one framework (FR2) sequence that must have a sequence identifier. Correction is required.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-9, 12-13, 16 and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitations of:

(i) "the sequence of aa 31-35 (CDR1), the sequence of aa 50-66 (CDR2), and the sequence of aa 99-106 (CDR3) of SEQ ID NO: 7" and "the sequence of aa 24-39 (CDR1), the sequence of aa 55-61 (CDR2), and the sequence of aa 94-102 (CDR3) of SEQ ID NO: 37" in claims 4(1)/(8) and 13(1)/(8),

(ii) "the sequence of aa 1-30 (FR1), the sequence of aa 36-49 (FR2), the sequence of aa 67-98 (FR3), and the sequence of aa 107-117 (FR4) of SEQ ID NO: 7" and "the sequence of aa 1-23 (FR1), the sequence of aa 40-54 (FR2), the sequence of aa 62-93 (FR3), and the sequence of aa 103-112 (FR4) of SEQ ID NO: 37" in claim 5(1)/(8), and

(iii) "the sequence of aa 1-234 of SEQ ID NO:73" in claim 16(1),

are indefinite because SEQ ID NOs: 7, 37 and 73 are an nucleic acid sequence and limited to their nucleic acid components. Applicants have failed to point out how a nucleic acid sequence would comprise the claimed amino acid sequence positions.

B. The recitation "which is a small antibody fragment" in claim 6 is indefinite. It is unclear if this "fragment" refers to any antibody fragment or it is limited to fragments containing the antigen-binding domain of the antibody.

C. The "(Hodgkin's disease, non-Hodgkin's lymphoma)" in claim 22 is ambiguous. It is unclear whether the diseases between the parenthesis are claimed or not.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-9, 12-13, 16 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody binding to human CD47, comprising the sequence of aa 31-35 (CDR1), the sequence of aa 50-66 (CDR2), and the sequence of aa 99-106 (CDR3) of SEQ ID NO: 93 and the sequence of aa 24-39 (CDR1), the sequence of aa 55-61 (CDR2), and the sequence of aa 94-102 (CDR3) of SEQ ID NO: 100, diabody thereof or the humanized antibody that binds to CD47 comprising SEQ ID NO: 110 or a therapeutic agent thereof, does not reasonably provide enablement for the humanized antibody claimed in claims 1-9, 12-13, 16 and 21-22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

This claim, given its broadest reasonable interpretation consistent with the instant specification, reads on the genus of fully human monoclonal anti-CD47 antibodies that comprise the heavy or light chain CDRs 1-3 of MABL-2 in the context of any non-specified framework and further paired with any non-specified VL that is capable of forming an CD47 antigen binding site in combination with the VH created from CRR1-3 of MABL-2 + framework residues.

The knowledge in the art of making the genus of fully human antibody that bind CD47 using a set of particular VH or VL CDRs as the starting point is low.

The specification discloses fully human monoclonal anti-CD47 antibodies derived from MABL-1 or MABL-2 which comprise defined VH and VL chains. The instant specification further discloses that the "MABL-2 antibody HL5", binds human CD47.

However, neither the instant specification nor the prior art provide sufficient guidance or direction for one of ordinary skill in the art to make the antibodies encompassed by the breadth of the instant claims.

The specification on page 42, lines 26-28 discloses that in selecting the human framework of MABL-2 was because amino acids in proximity to the CDRs may be greatly involved in binding to antigens. The specification on page 59, lines 16-18 discloses that the result suggests that FR2 is important and especially, amino acid residues near position 41 and 42 are essential for the improvement in activity. With respect to making the genus of fully human monoclonal antibodies that bind CD47 using a set of particular VH CDRs or VL CDRs as the starting point, e.g., claim 4(1) or 4(8), it is known in the art that antibody-antigen affinity and specificity is a function of not only direct CDR to antigen interactions, but also the interactions of the CDRs

with framework residues in the same chain, e.g., Vh CDR binding to Vh framework residues, and in the opposing chain, e.g., Vh CDR binding to Vl framework residues. In addition, the CDR residues of each chain can interact with the CDRs of the opposite chain. It is for this reason that antibody humanization protocols, e.g., humanization of a murine antibody, provide extensive guidelines as to the retention of certain murine residues in the context of the human framework so as to preserve this web of interactions, the loss of any one of these interactions having the potential to ablate antibody-antigen binding (see, e.g., Eduardo Padlan, Mol Immunol. 1994 Feb;31(3):169-217, in particular column bridging paragraph on page 177; page bridging paragraph pages 178-179 through page 180; pages 201, 204 and Tables 8, 22 and 23 and Adair et al., United States Patent No. 5,859,205, in particular columns 1-6, 9-11 and 27-28).

It is also known that given one specified variable domain, either heavy or light, the skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., J Immunol. 1993 Feb 1;150(3):880-7, see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain is used in the screening assay.

In the instant case, the claims recite only the 3 CDRs of a variable domain, not the variable domain itself. While CDRs are important for binding and contribute the majority of contact residues with the target antigen, the framework residues are also essential for maintaining the proper antigen-binding conformation of the CDRs and for proper association of the heavy and light chain variable regions.

As such, it appears that making the claimed genus of antibodies would be an unpredictable endeavor requiring far more than routine experimentation because 3 CDRs comprise less than a majority of the residues important for antigen recognition. Moreover, art techniques for identifying other variable domains by screening require an intact variable domain comprising CDRs interspersed between frameworks as the starting structure to be taken through the screening assay. The instant claims recite less than this minimum structure that is required for screening, and the instant specification fails to provide sufficient direction or guidance as to the breadth of the frameworks that can accommodate the claimed CDRs while simultaneously providing appropriate structure to pair with a light chain variable domain capable of acting with heavy chain variable domain to create an CD47 binding site.

Therefore, the skilled artisan would be unable to make the full breath of the genus of antibodies recited in the claims 4-5 and 13 without first performing additional, unpredictable research.

Further at issue is the claimed therapeutic agent for hematological disorders, the specification under Example 7 on pages 73-74 discloses the efficacy test of the humanized MABL-1 antibody sc(Fv)2 on leukemia model animals. However, no results were shown. Further, the specification under example 7(4) and Figure 21 evaluated the antitumor effect of humanized MABL-1, wherein humanized MABL-1 anti-CD47 antibodies were found to show antitumor effect. However, it is not clear that the antitumor effect of the humanized MABL-1present the

hematological disorders claimed.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

11. Claims 1-4, 6 and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by US 20030108546.

The `546 publication teaches and claims a single-chain Fv capable of inducing apoptosis of nucleated blood cells having Integrin Associated Protein (IAP) (claimed CD47) (see published claim 3), which is a humanized L chain V region (see published claim 11), which is a humanized H chain V region (see published claim 12). The `546 publication teaches a therapeutic agent for blood dyscrasia such as leukemia (see abstract). The `546 publication teaches preparation of Single-Chain Fv (scFv) of the reconstructed MABL-2 antibodies (see Example 5).

Claim 4 is included because a humanized VH or VL region of referenced MABL-2 would contained the claimed CDR1-3 of the VH and/or VL regions.

The reference teachings anticipate the claimed invention.

11. Claims 1- 4, 6-9, 12-13 and 21-22 are rejected under 35 U.S.C. 102(b)/(e) as being anticipated by US WO 0233073/20040242847.

Since the US `847 publication (English) claims priority to the `073 publication (Japanese), the rejection is made based on the English version of the Japanese publication.

The ` 847 publication teaches a method to modified antibodies whose H chain V regions and/or L chain V regions are humanized H chain V regions and/or humanized L chain V regions. Specifically, the humanized modified antibodies consist of the humanized L chain V region which comprises framework regions (FR) derived from an L chain V region of human monoclonal antibody and complementarity determining regions (hereinafter "CDR") derived from an L chain V region of non-human mammalian (e.g. mouse, rat, bovine, sheep, ape) monoclonal antibody and/or the humanized H chain V region which comprises FR derived from an H chain V region of human monoclonal antibody and CDR derived from an H chain V region of non-human mammalian (e.g. mouse, rat, bovine, sheep, ape) monoclonal antibody. In this case, the amino acid sequence of CDR and FR may be partially altered, e.g. deleted, replaced or added (see ¶37). Each V region of the modified antibody can be humanized by using conventional techniques. Once a DNA encoding each of humanized Fvs is prepared, a humanized single chain Fv, a fragment of the humanized single chain Fv, a humanized monoclonal antibody and a fragment of the humanized monoclonal antibody can readily be produced according to conventional methods. Preferably, amino acid sequences of the V regions thereof may be partially modified, if necessary (see ¶80). The `847 teaches vector pscM3Dem02 (see Figure 23), is constructed containing DNA encoding the H chain and L chain domains of a *humanized* mouse anti-human IAP (CD47) monoclonal antibody, *MABL-2*, separated by DNA encoding a GGGGSGGGGSGGGS linker peptide. The scFv antibody is strongly inhibitory of KPMM2 cell proliferation (Also see the English equivalent Abstract text of the `037 publication). The `847 publication teaches the production of the CHO cells constantly expressing MABL2-scFv, HL5, claimed as claimed in claim 4 (see ¶261-262, 264, Fig. 42-45).

Claim 4 is included because humanized mouse anti-CD47 monoclonal antibody MABL-2 inherently comprises the claimed CDRs.

The claimed diabody antibody of claims 7-9 and 12-13 are included because the `847 publication teaches shorter linkers that are less than five amino acids in length that would result in a diabody: the following are cited as example linkers: Ser, Gly-Ser, Gly-Gly-Ser, Ser-Gly-Gly, Gly-Gly-Gly-Ser, among others (see ¶66). The `847 publication teaches conventional crosslinking

radicals used for crosslinking peptides can be used as the crosslinking radicals to form the dimers. Examples are disulfide crosslinking by cysteine residue (see ¶31).

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-9, 12-17, 16 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20030108546, US WO 0233073 or US 20040242847, each in view of Sato et al (cancer Research 53:851-856, 1993.

The teachings of the `546 publication, `073 publication and the `847 publication has been discussed, supra. These publications disclose monoclonal antibody MABL-2, which has identical H and L chain CDRs to the claimed humanized antibodies. Further, the publications teach humanized antibodies including the humanization of MABL-2.

The reference teachings differ from the claimed invention only in the recitation of specific heavy and light FR1-4 in claim 5.

However, Sato et al teach that mouse antibodies are highly immunogenic in human patients. For this reason, their therapeutic value in human patients is limited. In order to be effective as therapeutic agents administered to human patients in repeated doses, mouse antibodies must be engineered to look like human antibodies. The most complete humanization of a mouse antibody is achieved by grafting the CDRs from the mouse antibody into a human antibody to recreate a good, functional antigen-binding site in a reshaped human antibody (page 851, 1st col., 2nd ¶). Sato et al teach that analysis of V-region sequence of the mouse PM-1 light and heavy chain variable regions belong to mouse kappa light chain subgroup I and mouse heavy chain subgroup II, respectively. with respect to human antibodies, the mouse PM-1 light and heavy chain variable regions were most similar to REI (72.2%), Member of human kappa light chain subgroup I and VAP (71.8), a member of human heavy chain subgroup II, respectively (see page 852, under Results). Sato et al teach that as shown in Fig. 3, two version fo reshaped human

PM-1 light chain variable region were designed. In version a, the human FRs were identical to the REI-based FRs present in the reshaped human CAMPATH-1H. REI is a member of subgroup I of human kappa light chain variable regions. Mouse PM-1 kappa light chain variable region is most similar to this human subgroup. Version b was based on version a with only one amino acid change at position 71 in human FR3. Residue 71 is part of the canonical structure for L1 and may, therefore, influence antigen binding. For the reshaped human PM-1 heavy chain variable region, six versions were designed. In all six versions, the human FRs were based on the NEW FRs present in reshaped human CAMPATH-1H. NEW is a member of subgroup II of human heavy chain variable regions and shows 68.4% similarity to mouse PM-1 heavy chain variable region . Seven amino acid residues in the human FRs (positions 1, 27, 28, 29, 30, 48, and 71) were identified as having a possible adverse influence on antigen binding. In the model of mouse PM-1 variable regions, residue 1 is a surface residue that is located close to the CDRs. Residues 27 to 30 are part of the canonical structure for Hl (31) and are observed in the PM-1 model to form part of the H l loop. These residues, therefore, are likely to be directly involved in antigen binding. Residue 48 is buried under the H2 loop and, therefore, may be influencing the conformation of this loop. Residue 71 is part of the canonical structure for H2 (31-33). In the model, it appeared that Arg-71 influences both the H1 and H2 loop conformations by forming hydrogen bonds with Thr-30, Asp-32, and Ser-54. See pag e852, under Design of Reshaped Human PM-1 variable Regions)

Sato et al. do not teach humanizing the specific antibodies of the instant invention, however, one of ordinary skill in the art at the time the invention was made would have been motivated to do so for any antibody intended for various therapeutic use in humans. The resultant humanized MABL-2 antibody would comprise the claimed FRs.

Therefore, from the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be

obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 18, 2009

/Maher M. Haddad/
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